SEQUENCE LISTING

<110> WOULFE, SUSAN L.
      JAIN, RITA
      BURR, AIMEE

<120> ENGINEERED FAB' FRAGMENT ANTI-TUMOR
  NECROSIS FACTOR ALPHA IN COMBINATION WITH DISEASE MODIFYING
  ANTI-RHEUMATIC DRUGS

<130> 122294-1010

<140> US/10/728,420

<141> 2003-12-05

<150> US 60/431,053

<151> 2002-12-05

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<400> 1
Asp Tyr Gly Met Asn
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<223> Mouse monoclonal antibody hTNF40/human hybrid CDRH2

<400> 2
Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Ala Asp Ser Val Lys
 1   5   10   15
Gly

<210> 3
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<220>
<223> Mouse monoclonal antibody hTNF40 CDRH3

<400> 3
Gly Tyr Arg Ser Tyr Ala Met Asp Tyr
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<210> 4
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<220>
<223> Mouse monoclonal antibody hTNF40 CDRL1

<400> 4
Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
 1   5   10

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<400> 5
Ser Ala Ser Phe Leu Tyr Ser
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<220>
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<400> 6
Gln Gln Tyr Asn Ile Tyr Pro Leu Thr
 1   5

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Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Val Asp Asp Phe Lys
1   5   10   15
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<220>
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<222> (1)...(321)
<223> Synthetic hTNF40-gL1

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

gac cgg gtc acc atc act tgt aaa gcc agt cag aac gta ggt act aac   96
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20   25   30

gta gcc tgg tat cag caa aaa cca ggt aaa gcc cca aaa gcc ctc atc   144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
        35   40   45

tac agt gcc tct ttc ctc tat agt ggt gta cca tac agg ttc agc gga   192
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Tyr Arg Phe Ser Gly
    50   55   60

tcc ggt agt ggt act gat ttc acc ctc acg atc agt agc ctc cag cca   240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

gaa gat ttc gcc act tat tac tgt caa cag tat aac atc tac cca ctc   288
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Leu
                85   90   95

aca ttc ggt cag ggt act aaa gta gaa atc aaa   321
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
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<210> 11

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<222> (1)...(354)
<223> Synthetic gh3hTNF40.4

<223> Grafted Heavy Chain for Modified Fab

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 1               5                  10                  15

tca ctg aga ttg tcc tgt gct gca tct ggt tac gtc ttc aca gac tat      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Val Phe Thr Asp Tyr
            20                  25                  30

gga atg aat tgg gtt aga cag gcc ccg gga aag ggc ctg gaa tgg atg     144
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

ggt tgg att aat act tac att gga gag cct att tat gct gac agc gtc     192
Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Ala Asp Ser Val
    50                  55                  60

aag ggc aga ttc acg ttc tct cta gac aca tcc aag tca aca gca tac     240
Lys Gly Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
 65                  70                  75                  80

ctc caa atg aat agc ctg aga gca gag gac acc gca gtg tac tat tgt     288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gct aga gga tac aga tct tat gcc atg gac tac tgg ggc cag ggt acc     336
Ala Arg Gly Tyr Arg Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
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cta gtc aca gtc tcc tca                                             354
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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15
Asp Arg Val Thr Ile Thr Cys
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<210> 84
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<223> Human hTNF40 framework L1

<400> 84
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1   5   10   15
Asp Arg Val Ser Val Thr Cys
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<210> 85
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<212> PRT
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<400> 85
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1   5   10   15

<210> 86
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<212> PRT
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<220>
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<400> 86
Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile Tyr
1   5   10   15

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<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> human group 1 consensus framework L3

<400> 87
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1               5                  10                  15
Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
            20                  25                  30


<210> 88
<211> 32
<212> PRT
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<220>
<223> Human hTNF40 framework L3

<400> 88
Gly Val Pro Tyr Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1               5                  10                  15

Leu Thr Ile Ser Thr Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys
            20                  25                  30


<210> 89
<211> 11
<212> PRT
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<220>
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<400> 89
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 1               5                  10


<210> 90
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Human hTNF40 framework L4

<400> 90
Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
 1               5                  10
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<210> 91
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
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<400> 91
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
            20   25   30

<210> 92
<211> 30
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<220>
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<400> 92
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1   5   10   15
Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Val Phe Thr
            20   25   30

<210> 93
<211> 14
<212> PRT
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<220>
<223> human group 1 consensus framework H2

<400> 93
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
1   5   10

<210> 94
<211> 14
<212> PRT
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<220>
<223> Human hTNF40 framework H2

<400> 94
Trp Val Lys Gln Ala Pro Gly Lys Ala Phe Lys Trp Met Gly
1   5   10

<210> 95
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<212> PRT
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<220>
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Arg Val Thr Ile Thr Arg Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu
 1   5   10   15
Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            20   25   30

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<220>
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<400> 96
Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe Leu Gln
 1   5   10   15
Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
            20   25   30

<210> 97
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<212> PRT
<213> Artificial Sequence

<220>
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<400> 97
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 1   5   10

<210> 98
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<212> PRT
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<220>
<223> human group 1 consensus framework H4

<400> 98
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 1   5   10

<210> 99

<211> 324
<212> DNA
<213> murine

<220>
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<222> (1)...(324)
<223> mouse hTNF40 light chain variable domain

<400> 99
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gac att gtg atg acc cag tct caa aaa ttc atg tcc aca tca gta gga    48
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
 1               5                  10                  15

gac agg gtc agc gtc acc tgc aag gcc agt cag aat gtg ggt act aat    96
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
                20                  25                  30

gta gcc tgg tat caa cag aaa cca gga caa tct cct aaa gca ctg aat   144
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Asn
            35                  40                  45

tac tcg gca tcc ttc cta tat agt gga gtc cct tat cgc ttc aca ggc   192
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Tyr Arg Phe Thr Gly
        50                  55                  60

agt gga tct ggg aca gat ttc act ctc acc atc agc act gtg cag tct   240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Thr Val Gln Ser
 65                  70                  75                  80

gaa gac ttg gca gag tat ttc tgt cag caa tat aac atc tat cct ctc   288
Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ile Tyr Pro Leu
                85                  90                  95

acg ttc ggt gct ggg acc aag ctg gag ctg aaa cgt                   324
Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
                100                 105
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<210> 100
<211> 354
<212> DNA
<213> murine

<220>
<221> CDS
<222> (1)...(354)
<223> mouse hTNF40 heavy chain variable domain

<400> 100
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cag atc cag ttg gtg cag tct gga cct gag ctg aag aag cct gga gag    48
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
 1               5                  10                  15

aca gtc aag atc tcc tgc aag gct tct gga tat gtt ttc aca gac tat    96
Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Val Phe Thr Asp Tyr
                20                  25                  30
```

```
gga atg aat tgg gtg aag cag gct cca gga aag gct ttc aag tgg atg      144
Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Ala Phe Lys Trp Met
        35                      40                      45

ggc tgg ata aac acc tac att gga gag cca ata tat gtt gat gac ttc      192
Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Val Asp Asp Phe
    50                      55                      60

aag gga cga ttt gcc ttc tct ttg gaa acc tct gcc agc act gcc ttt      240
Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Phe
 65                      70                      75                  80

ttg cag atc aac aac ctc aaa aat gag gac acg gct aca tat ttc tgt      288
Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
                    85                      90                      95

gca aga ggt tac cgg tcc tat gct atg gac tac tgg ggt caa gga acc      336
Ala Arg Gly Tyr Arg Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                     105                     110

tca gtc acc gtc tct tca                                              354
Ser Val Thr Val Ser Ser
        115


<210> 101
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<220>
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<222> (29)...(0)
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cttggctctg acgtacgagt cagg                                         84


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<212> DNA
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<220>
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<223> IGS cassette-1
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<400> 102

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  Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys    Met Lys
   1               5                   10                    15

aag act gct ata gca att g                                          67
Lys Thr Ala Ile Ala Ile
                20
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<210> 103
<211> 69
<212> DNA
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<220>
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<222> (45)...(68)

<223> IGS cassette-2

<400> 103

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g agc tca cca gta aca aaa agt ttt aat aga ggg gag tgt taa         43
  Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys    *
   1               5                   10

a atg aag aag act gct ata gca att g                                69
  Met Lys Lys Thr Ala Ile Ala Ile
       15                 20
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<210> 104
<211> 81
<212> DNA
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<220>
<221> CDS
<222> (2)...(43)

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<222> (57)...(80)

<223> IGS cassette-3

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g agc tca cca gta aca aaa agc ttt aat aga gga gag tgt tga         43
  Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys    *
   1               5                   10

ggaggaaaaa aaa atg aag aaa act gct ata gca att g                   81
                Met Lys Lys Thr Ala Ile Ala Ile
                 15                 20
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<210> 105
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<222> (2)...(43)

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<223> IGS cassette-4

<400> 105
g agc tca cca gta aca aaa agt ttt aat aga gga gag tgt tga                43
  Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  *
   1               5                   10


cgaggattat ata atg aag aaa act gct ata gca att g                         81
           Met Lys Lys Thr Ala Ile Ala Ile
                15                   20



<210> 106
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> human group 3 consensus framework H1

<400> 106
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
            20                  25                  30



<210> 107
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<212> PRT
<213> Artificial Sequence

<220>
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<400> 107
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
 1               5                   10



<210> 108
<211> 32
<212> PRT
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<213> Artificial Sequence

<220>
<223> human group 3 consensus framework H3

<400> 108
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 1   5   10   15
Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
            20   25   30

<210> 109
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<212> PRT
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<220>
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<210> 113
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<220>
<223> Synthetic CDP870 Light chain mature protein sequence

<400> 113
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20   25   30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
        35   40   45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Tyr Arg Phe Ser Gly
    50   55   60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                      80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Leu
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
            165                 170                 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205
Phe Asn Arg Gly Glu Cys
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<210> 114
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<210> 115
<211> 229
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic CDP870 Heavy chain mature protein sequence

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Val Phe Thr Asp Tyr
            20                  25                  30
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met

            35                  40                  45
Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
65                  70                  75                      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Gly Tyr Arg Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110
Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160
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Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165   170   175
Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180   185   190
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195   200   205
Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
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His Thr Cys Ala Ala
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<210> 116
<211> 1477
<212> DNA
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<220>
<223> Synthetic CDP870 nucleic acid sequence (sense strand)

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gctgacattc aaatgaccca gagcccatcc agcctgagcg catctgtagg agaccgggtc 120
accatcactt gtaaagccag tcagaacgta ggtactaacg tagcctggta tcagcaaaaa 180
ccaggtaaag ccccaaaagc cctcatctac agtgcctctt tcctctatag tggtgtacca 240
tacaggttca gcggatccgg tagtggtact gatttcaccc tcacgactag tagcctccag 300
ccagaagatt tcgccactta ttactgtcaa cagtataaca tctacccact cacattcggt 360
cagggtacta agtagaaat caaacgtacg gtagcggccc catctgtctt catcttcccg 420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 480
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 540
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 600
acgctgagga aagcagacta cgagaaacac aaagcttacg cctgcgaagt cacccatcag 660
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